Chemical Engineering Science 107 (2014) 76–92

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

A mechanistic population balance model for granulation processes: Effect of process and formulation parameters

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HIGHLIGHTS

- A semi-mechanistic aggregation kernel for a granulation process is proposed.
- Qualitative model validation integrating key granulation mechanisms is performed.
- A detailed sensitivity analysis is performed to analyze the effect of the proposed kernel.

ARTICLE INFO

Article history:
Received 1 October 2013
Received in revised form
9 November 2013
Accepted 16 November 2013
Available online 23 November 2013

Keywords:
Granulation
Multi-dimensional population balance model
Induction growth
Mechanistic model
Aggregation kernel

ABSTRACT

This work is concerned with the theoretical development of a semi-mechanistic aggregation kernel in a population balance model (PBM) which takes into account the effect of droplet spreading on a particle surface that aids in the coalescence of particles. Empirical aggregation kernels are more commonly used in simulations however they do not reflect the true physics of the system. The proposed kernel is computationally less expensive, yet it takes into account the various key operating parameters that affect the process. The kernel has been validated qualitatively and the lumped and distributed properties show good agreement with the expected behavior of the process. The various empirical parameters present in the granulation model have been identified and expressed as a function of the measurable operating quantities, thus providing a better knowledge regarding the effect of the process parameters on the final product with the help of a more fundamental, first principle based model. A detailed sensitivity analysis (involving viscosity, impeller speed, contact angle and liquid spray rate) has also been conducted in order to study the influence of the process parameters on the final granule properties. This knowledge provides a theoretical basis for the high-shear wet granulation process design space development. The model has also been able to successfully capture the steady and induction behavior of the process under the expected operating conditions.

1. Introduction

Wet granulation is a crucial particle design process relevant to various particulate industries, which involves agglomeration of fine powder to form larger granules with the addition of external binder (Iveson et al., 2001). Due to the lack of scientific knowledge in processes involving solids, granulation is often carried out very inefficiently in the industry with large recycle ratios (Salman et al., 2007). This reinforces the need to develop higher fidelity models in order to obtain better process knowledge, higher predictability and improved control and operation of the granulation process. For instance, the proper regulation and control of such particulate processes in the pharmaceutical industry is of critical importance due to the imposition of a tight quality criteria by the regulating authorities (Boukouvala et al., 2011).

Using population balance models (PBMs) to model particulate processes such as granulation is a well accepted practice prevalent in the scientific community (Litster, 2003; Iveson et al., 2001; Ramachandran and Barton, 2010). The advantage of PBMs over other modeling approaches is the discrete nature of the PBEs which can very well capture the physics of the particulate processes in a convenient equation based mathematical framework. Various other approaches used for the purpose of modeling granulation processes include Discrete Element Modeling (DEM) (Gantt et al., 2006; Maio and Renzo, 2007), hybrid model combining the volume of fluid approach with PBM (Stepanek and Rajniak, 2006) or Computational Fluid Dynamics (CFD) with PBM (Rajniak et al., 2009). PBMs can be solved using various approaches such as

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http://dx.doi.org/10.1016/j.ces.2013.11.031

finite volume methods (Chaudhury and Ramachandran, 2013), finite difference methods, finite element methods (Mantzaris et al., 2001), the method of classes (Alopaeus et al., 2006), the method of moments (Hulburt and Katz, 1964; Marchisio et al., 2003; Qamar et al., 2010), the method of characteristics (Mesbah et al., 2009), high resolution algorithms (LeVeque, 2002), hierarchical two tier technique (Immanuel and Doyle III, 2003; Pinto et al., 2007), Lattice Boltzmann approach (Majumder et al., 2012), Monte Carlo methods (Braumann et al., 2010; Marshall Jr. et al., 2011). Reduced order PBMs have also been studied by reducing the multidimensional PBM into multiple one-dimensional PBMs using the marginal distribution approach in order to obtain an equivalent system with less complicated numerical solutions (Hounslow et al., 2001; Biggs et al., 2003). Other works aimed at reducing the computational complexity in solving PBMs include obtaining lumped models (Barrasso and Ramachandran, 2012), employing parallel computations (Prakash et al., 2013a, 2013b). Many one dimensional PBMs have been reported in literature (Sastry, 1975) which usually utilize granule size as the only independent property affecting the granule growth behavior. The limitation of considering one-dimensional models has been previously reported by Iveson (2002). He suggested that granule binder, porosity and in some cases, composition can vary between granules and are thus needed to be addressed with the use of multidimensional PBMs along with the appropriate choice of internal coordinates and more accurate submodels.

The multidimensional PBM is formulated based on the individual solid, liquid and gas volumes as the internal coordinates in order to enable decoupling of the integrated process with respect to the individual mesoscopic subprocesses (Verkoeijen et al., 2002). The various underlying mechanisms governing granulation, such as aggregation, breakage, drying/rewetting, consolidation, layering, have strong interactions with each other (Iveson, 2002). Most models observed in the literature have failed in tracking the induction behavior that exist in the granulation process. There is also a lack of models which can effectively address the interactions between the various subprocesses affecting the final outcome of granulation. Immanuel and Doyle III (2005) and Ramachandran et al. (2009) had proposed a mechanistic kernel for aggregation and breakage respectively.

The importance of multidimensional PBMs is well documented (Iveson et al., 2001), but developing the model in a way, such that, the interactions can be tracked effectively, is a more challenging task. The significance of binder content in the growth of granules is associated with the fact that with higher amount of the binder, there is a larger availability of surface-wet granules (Knight et al., 1993) and that enhances the aggregation of finer particles (Link and Schlunder, 1997). As for the granule porosity, below a certain critical porosity, liquid is squeezed onto the surface, thus resulting in surface-wet granules which help promote granule growth, hence porosity is an important particle trait that needs to be characterized (Ramachandran et al., 2008). With the progress of consolidation, more liquid is forced to squeeze out of the pores thus providing an increased surface liquid availability. So, as the impeller speed increases, the consolidation of particles increases and so does the aggregation and the breakage. The system is observed to exhibit steady growth when aggregation is more dominant. On the contrary, a system where aggregation is not dominant is prone to exhibiting induction behavior (as aggregation is catalyzed with the liquid being squeezed out of the pores as consolidation proceeds) under high consolidation (Walker, 2007).

One of the major drawbacks of using PBMs to quantify the behavior of the granulation process is the potential usage of empirical parameters. It is very important to use more mechanistic equations in order to have a more first principle based predictive model. Empirical aggregation and breakage kernels have been more commonly observed in literature, but these kernels can neither be used for extrapolating the system behavior under different operating conditions nor be utilized for predictive understanding of the process. Immanuel and Doyle III (2005) had proposed a mechanistic kernel, based on the coalescence mechanisms identified by Liu et al. (2000), which can be considered to be a more fundamental representation of the granulation process as it takes into account the effect of key material properties and process parameters. The proposed mechanistic kernel was however computationally expensive and also did not consider the effect of contact angle on the granulation outcome. Various other experimental studies have been carried out in order to link the process variables and various microscopic properties of the particles with the granulation process (Liu et al., 2000; Stepanek and Rajniak, 2006). Similarly, a more fundamental breakage kernel was proposed by Ramachandran et al. (2009) which gives a better insight into the breakage mechanism. The breakage kernel took various process parameters into consideration and represented the kernel as a ratio of external stress and the intrinsic strength. The stresses were calculated from various forces acting on the particle (particle–particle, particle–wall, particle–fluid). Since an established mechanistic kernel for breakage is available, breakage has not been taken into consideration in this work so that the ability of the aggregation kernel to track experimental observations can be studied.

2. Objectives

The main impetus behind this work is to connect the interactions between the mechanisms influencing granulation so that a better physical representation (compared to the pre-existing empirical kernels) can be derived which can also enable improved control studies. Therefore, these mechanisms can be said to be affected by the more fundamental operating properties such as impeller speed, granulator geometry and binder properties. The objectives of this paper are as follows:

- Identification and correlation between the crucial operating parameters (measurable) that affect the final granule properties.
- Propose a semi-mechanistic aggregation kernel involving low computational overheads which can adequately capture the system behavior.
- Decouple the effect of aggregation and consolidation such that the model is capable of capturing the induction behavior of the system.

3. Background

The 3-D PBM, based on our previous works (Ramachandran and Barton, 2010; Ramachandran et al., 2012; Barrasso et al., 2013; Chaudhury et al., 2012; Chaudhury and Ramachandran, 2013), describing granulation process can be written as

$$\frac{\partial}{\partial t}F(s,l,g,t)+\frac{\partial}{\partial g}\left[F(s,l,g,t)\frac{dg}{dt}\right]+\frac{\partial}{\partial s}\left[F(s,l,g,t)\frac{ds}{dt}\right] +\frac{\partial}{\partial l}\left[F(s,l,g,t)\frac{dl}{dt}\right]=\Re_{agg}+\Re_{break}+\Re_{nuc} \tag{1}$$

where $F(s,l,g,t)$ represents the population density function. The solid, liquid and gas volumes have been represented with the variables s, l and g respectively. The respective partial derivative terms represent the various growth mechanisms—layering, rewetting/drying and consolidation, associated with the granulation